Guidance for Industry

Internal Radioactive Contamination — Development of Decorporation Agents

DRAFT GUIDANCE

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U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)

February 2005
Clinical Medical

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Internal Radioactive Contamination — Development of Decorporation Agents

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Internal Radioactive Contamination — Development of Decorporation Agents

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I. INTRODUCTION

This document provides guidance to industry on the development of decorporation agents for which evidence is needed to demonstrate effectiveness but for which human efficacy studies are unethical or infeasible. In such instances, the *Animal Efficacy Rule*, 21 C.F.R. Part 314 Subpart I, may be invoked to approve new medical products not previously marketed or new indications for previously marketed products. Specifically, this document provides guidance on (1) chemistry, manufacturing and controls (CMC) information, (2) animal efficacy, safety pharmacology, and toxicology studies, (3) clinical pharmacology, biopharmaceutics, and human safety studies, and (4) postapproval commitments, for such products.

FDA's guidance documents, including this guidance, do not establish legally enforceable responsibilities. Instead, guidances describe the Agency's current thinking on a topic and should be viewed only as recommendations, unless specific regulatory or statutory requirements are cited. The use of the word *should* in Agency guidances means that something is suggested or recommended, but not required.

II. BACKGROUND

Internal radioactive contamination can arise from accidents involving nuclear reactors, industrial sources, or medical sources. The potential for such accidents has been present for many years. Recent events also have highlighted the potential for nonaccidental radioactive contamination as a result of malicious, criminal, or terrorist actions. Internal contamination occurs when

[1] This draft guidance has been prepared by the Radioeliminators Working Group, which includes members from the Center for Drug Evaluation and Research (CDER) and the Center for Biologics Evaluation and Research (CBER) at the Food and Drug Administration.

radioactive material is ingested, inhaled, or absorbed from a contaminated wound. As long as these radioactive contaminants remain in the body, they may pose significant health risks. The risks are largely long term in nature and depend not only on the type and concentration of the radioactive contaminant absorbed, but also on the health status of the exposed individual. The potential for development of cancers of the lung, liver, thyroid, stomach, and bone, among others, are principal long-term health concerns, as are fibrotic changes in tissues such as lung, which may lead to restrictive lung disease and other chronic debilitating conditions. The only effective method of reducing these risks is removal of the radioactive contaminants from the body.[2] The long latency of these conditions means that evaluation and treatment of internal contamination should not take precedence over treatment of conventional injuries that may be acutely life-threatening. However, early recognition of internal contamination provides the greatest opportunity for radiocontaminant removal.[2]

For the purposes of this guidance, the term *decorporation agents* refers to medical products[3] that increase the rate of elimination or excretion of absorbed, inhaled, or ingested radioactive contaminants. The effectiveness of most decorporation agents for the treatment of internal radioactive contamination cannot be tested in humans because the occurrence of accidental or nonaccidental radioactive contamination is rare, and it would be unethical to deliberately contaminate humans with potentially harmful amounts of radioactive materials for investigational purposes.

A. Radiation Contamination Scenarios

A *radiological dispersal device* (RDD) (sometimes called a "dirty bomb") is a device that causes the purposeful dissemination of radioactive material across an area using conventional (nonnuclear) explosives. The material dispersed could originate from any location that uses radioactive sources, such as a nuclear power plant, an industrial complex, or medical and research facilities. The radioactive material would be scattered as radioactive debris across an area that depends on the size of the explosive and how high above the ground the detonation occurs. Considering radioactive half-life and commercial availability, some of the radioactive contaminants that might be used in an RDD include strontium-90, cobalt-60, cesium-137, iridium-192, radium-226, and americium-241. Within the blast zone, this type of weapon would cause conventional blast casualties contaminated with radioactive material and would complicate medical evacuation within the contaminated area. In addition, individuals outside the conventional blast zone, including rescue workers, would be at risk for internal contamination through inhalation of radioactive debris if not properly protected.

Significant amounts of radioactive material may be deposited on surfaces not only through RDDs but also through the use of a nuclear weapon, the destruction of a nuclear reactor, or an industrial or military nuclear accident. Persons living or working in contaminated areas could

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[2] *See* National Council on Radiation Protection and Measurements (1980), *Management of Persons Accidentally Contaminated With Radionuclides,*(NCRP Report 65), Washington, DC, National Council on Radiation Protection and Measurements, for additional information on management of internal radioactive contamination.

[3] For ease of reference, this guidance uses the term *product* to refer to all products (excluding blood products) regulated by CDER. Similarly, for ease of reference, this draft guidance uses the term *approval* to refer to both drug approval and biologic licensure.

receive sufficient radioactive contamination to suffer acute symptoms of radiation injury and could develop late sequelae such as cancer or genetic damage.

B. Uptake and Clearance of Radioactive Contaminants

The uptake and retention of a radioactive contaminant is influenced by its portal of entry, chemistry, solubility, metabolism, and particle size.[2,4,5] Internal contamination occurs by three main routes: inhalation, ingestion, and wound contamination. A fourth and infrequent route is percutaneous absorption, which applies almost exclusively to radioactive tritium in association with water.

Of the exposure routes, inhalation poses the greatest threat, especially in a fallout environment.[2,4,5] The size of the radioactive particle influences lung deposition, because particles with an aerodynamic diameter greater than 10 microns tend to be deposited in the upper respiratory tract. Particles that are deposited in the lower respiratory tract may be more easily absorbed into the body and later taken up by target organs. Insoluble particles (especially plutonium from unspent fuel or industrial accidents) pose a particular threat to the lung because prolonged exposure of the lower respiratory tract to alpha emitters such as plutonium causes an increased incidence of pulmonary malignancy.[4,6] Depending on the aerodynamic diameter of the particles and other factors, about 25 percent of inhaled radioactive particles may be immediately exhaled, leaving the remaining 75 percent to be deposited along the respiratory tree.[2] About half of the retained particles are deposited in the upper bronchial tree, where they are moved by the ciliary epithelium to the nasopharynx, where some may be expectorated but some are swallowed, thereby entering the gastrointestinal path. Ingestion is thus usually secondary to inhalation, but direct ingestion from contaminated foodstuffs may also occur. The degree of intraluminal gastrointestinal exposure and possible absorption of certain radioactive contaminants depends on transit time through the gut, which will vary widely from person to person.[2,5] The much slower rate of movement in the large intestine places its luminal lining at higher risk for damage from nonabsorbed radiocontaminants. Gastrointestinal transit time may be shortened by use of emetic and/or purgative agents.

Some relatively soluble radioactive contaminants may not be absorbed due to acidic or caustic properties that fix them to tissue proteins.[2] Systemic absorption through the intestine varies widely, depending on the radioactive contaminant and its chemical form and characteristics. For instance, clear differences exist between radioiodine, which is rapidly and completely absorbed, and plutonium, which is not absorbed to any appreciable extent (0.003 percent).[2] The gastrointestinal tract is the critical target organ for the many insoluble radioactive contaminants that travel its length almost unabsorbed.

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[4] See Durakovic, A (1987), Internal Contamination with Medically Significant Radionuclides. In *Military Radiobiology*, edited by JJ Conklin and RI Walker, 241-264, Orlando, FL, Academic Press.

[5] See Cerveny, TJ (1988), Treatment of Internal Radionuclide Contamination. In *Medical Consequences of Nuclear War*, edited by RI Walker and TJ Cerveny, 55-65, Falls Church, VA, TMM Publications, Office of the Surgeon General.

[6] See Jarrett, DG (1999), *Medical Management of Radiological Casualties*, Bethesda, MD, Armed Forces Radiobiology Research Institute.

Wounds contaminated by fallout and shrapnel may provide continuous irradiation of surrounding tissues and increase the likelihood of systemic incorporation.[2,5,6] This hazard remains until the contaminant is removed by irrigation, surgical debridement, or decay.

C. Management of External Radioactive Contamination

Radioactive contamination of the skin is usually not immediately life-threatening to either the patient or medical personnel, especially after the removal of clothing and external decontamination, unless the dose rate is several Gray (Gy) per hour.

Following the removal of clothing and external decontamination, evaluation and monitoring by a medical professional or health physicist should be performed as soon as possible to provide qualitative and quantitative information about residual external contamination as well as internal contamination.[2] If the external radioactive contaminant persists in spite of initial washing with soap or detergent and water, further decontamination should be supervised by an appropriately trained physician.[2]

D. Treatment of Internal Radioactive Contamination

The goals of internal decontamination are to reduce absorption and to enhance excretion of radioactive contaminants. Treatment is most effective if it is started as soon as possible after contamination. Radioactive contaminants may be internalized via inhalation, ingestion, or through wounds and skin. Treatment should be directed by knowledge of the specific radiocontaminant. Ideally, internal decontamination should begin during the first few hours if the treating physician suspects that radiocontaminants may have been internalized. Currently, as discussed below, Prussian blue, KI, Ca-DTPA and Zn-DTPA, when manufactured under conditions specified in an approved NDA, have been found safe and effective for the treatment of internal contamination with radioactive cesium, iodine, and plutonium, americium, or curium, respectively. Currently, Prussian blue, potassium iodide, and Ca- and Zn-DTPA are approved products in the United States.

1. General Principles

Early information on the history of the incident may identify the major radioactive contaminants involved and provide some dosimetry information. Patients will likely present with no clinical symptoms of contamination, but may have sustained burns, lacerations, or other more serious trauma. Immediate treatment for physical injuries should be initiated to stabilize the patient. After the patient is stabilized, critical decisions on initiating treatment for internal radioactive contamination will need to be made based on historical information (to determine the level of contamination and the possible radiocontaminants involved), as well as knowledge of the metabolism of the radiocontaminants, human physiology, and the pharmacology of available treatments. Treatment for internal contamination should begin as soon as possible after contamination,[2,4,5,7,8] and appropriate monitoring for excretion of radiocontaminants (a measure

[7] See Commission of European Communities Radiation Protection Program (2000), Decorporation of Radionuclides from the Human Body. Edited by MH Henge-Napoli, GN Stradling, and DM Taylor. *Radiat Prot Dosimetry* 87:1-57

of treatment efficacy) should follow. Radiation dose estimates obtained by appropriate whole-body counting, by bioassay or biodosimetry, or by urinary or fecal sampling, may be used to determine the treatment course. If feasible and the route of elimination is known, it is helpful to obtain a baseline measurement of radiation excretion.

Physicochemical properties of radiocontaminants will play a significant role in determining treatment. The solubility of the contaminant may determine its absorption and distribution within the body. Because most potential contaminants are at least partially soluble, some small fraction of the contaminant will usually become internalized from the lung or through a wound. On the other hand, normally soluble materials may be present in an insoluble form, or may become insoluble under systemic physiological conditions. Therefore, without initial knowledge of the identity of the contaminant or its solubility, treatment based on an estimate of the most probable radiocontaminants present should begin as soon as possible to significantly increase the probability of successful internal decontamination.[2,4,5,7]

In a complete nuclear detonation (e.g., a complete fission event), more than 400 radioactive contaminants would be released. Of these, only about 40 are potentially hazardous to humans.[2,4,5] The most significant radiocontaminants from unspent nuclear fuel (potentially used in an RDD) or nuclear weapons accidents are tritium, plutonium, and uranium. Radiocontaminants of immediate medical significance are listed in Table 1, with descriptions of their properties, target organs, and treatment (either with an FDA approved product or as suggested in the literature).

2. The Gastrointestinal Tract as a Route of Elimination

It may be appropriate to remove or enhance transit of gastrointestinal contents after radioactive contamination if contamination has recently occurred via ingestion. It is recommended that the current standard of care as it applies to other poisonings and overdoses by the oral route be used unless consciousness is impaired or ingestion of corrosive agents has occurred.

Certain nonabsorbed binding resins may have utility in inhibiting the uptake of radioactive contaminants in the gut. For example, Prussian blue, a nonabsorbed pigmented resin, has been used since the 1960s as an investigational agent administered orally to enhance the fecal excretion of cesium and thallium by means of ion exchange. Prussian blue was used to treat victims in the 1987 cesium-137 contamination incident in Goiânia[9,10] and has been well tolerated in humans.[2,4,11,12] In Goiânia, contamination occurred primarily via the oral route, but the

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[8] See Waller EA, Stodilka RZ, Leach K, and Prud'homme-Lalonde (2002), *Literature Survey on Decorporation of Radionuclides from the Human Body*, Ottowa, Defense R&D Canada Technical Memorandum TM 2002-042.

[9] See Farina, R, Brandao-Mello, CE, and Oliveira, AR (1991), Medical Aspects of ^{137}Cs Decorporation: The Goiania Radiological Accident. *Health Physics* 60:63-66.

[10] See Melo DR, Lipzstein, JL, de Oliveira, CAN, and Bertelli, L (1994), ^{137}Cs Internal Contamination Involving a Brazilian Accident, and the Efficacy of Prussian Blue Treatment, *Health Physics* 66:245-252.

[11] See Volf, V (1978), *Treatment of Incorporated Transuranium Elements.* Vienna, International Atomic Energy Technical Reports Series No. 184.

radiocontaminant was no longer present in the GI tract in substantial amounts when treatment with Prussian blue was begun. Prussian blue may be continued for 30 days or longer, as dictated by the level of contamination; it was used for prolonged periods in several of the Goiânia casualties.

After review of the published literature and other available data, FDA concluded in 2003 that Prussian blue, when produced under conditions specified in approved new drug applications (NDAs), is safe and effective for the treatment of internal contamination with radioactive thallium, nonradioactive thallium, or radioactive cesium.[13] At the same time, FDA announced the availability of a guidance document, *Prussian Blue Drug Products: Submitting a New Drug Application,* to assist manufacturers who plan to submit NDAs for Prussian blue. One manufacturer (HEYL Chemisch-pharmazeutische Fabrik GmbH & Co. KG) has since received approval for its Prussian blue product (Radiogardase).

There are suggestions in the literature that other nonabsorbed binding resins, such as sodium polystyrene sulfonate, may also have utility in inhibiting the uptake of radioactive contaminants in the gut.[2] Sodium polystyrene sulfonate is approved in the United States under the name Kayexelate but is not approved as a decorporation agent.

Aluminum-containing antacids are relatively well-tolerated and have been recommended for reducing the absorption of radioactive strontium.[2,4] There are preliminary data to suggest that either aluminum phosphate gel or aluminum hydroxide, given immediately after exposure, may decrease the absorption of radioactive strontium in the gut. [2,4] The efficacy of these products as potential decorporation agents has not been established, however, and none is approved in the United States for that indication.

3. Prevention or Reversal of Radiocontaminant Interaction with Tissues

a. Blocking and Diluting Agents

For radiocontaminants already in the blood, *blocking and diluting agents* will reduce uptake at target tissues. Administering a blocking agent such as potassium iodide (KI) allows for saturation of metabolic processes in the thyroid with stable, nonradioactive iodine thereby preventing uptake of radioactive iodine. In 1978, FDA announced its conclusion that KI is safe and effective for use as a blocking agent to prevent the uptake of radioactive iodine by the thyroid in a radiation emergency under certain specified conditions of use.[14] In 1982, FDA announced its final recommendations on the administration of KI to the general public in a radiation emergency.[15] These recommendations were formulated after reviewing studies relating radiation dose to risk

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[12] See Fasiska, BC, Bohning, DE, Brodsky, A, and Horm, J (1971), Urinary Excretion of ^{241}Am Under DTPA Therapy, *Health Physics* 21:523-529

[13] See the *Federal Register,* Vol. 68, p. 5645, February 4, 2003.

[14] See the *Federal Register*, Vol. 43, p. 58798, December 15, 1978.

[15] See the *Federal Register*, Vol. 47, p. 28158 June 29, 1982.

of thyroid disease. FDA relied on estimates of external thyroid irradiation after the nuclear detonations at Hiroshima and Nagasaki and analogous studies among children who received therapeutic radiation to the head and neck. The agency concluded that, at a projected dose to the thyroid of 25 cGy or greater from ingested or inhaled radioactive iodine, the benefits of short-term use of small quantities of KI outweighed the potential risk of thyroid cancer.

In 2001, after careful review of the data from the Chernobyl accident relating estimated thyroid radiation dose and cancer risk in exposed children, FDA revised its recommendation for administration of KI based on age, predicted thyroid exposure, and pregnancy and lactation status.[16] In its revised guidance, FDA emphasized that KI should be used as an adjunct to evacuation (although that may not always be feasible), sheltering, and control of foodstuffs. [17]

Dilution is achieved by the administration of large quantities of the stable, nonradioactive isotope so that incorporation of the radioactive contaminant is minimized. As an example, forced hydration can increase the excretion of tritium.[2] For maximum effectiveness, the stable isotopes that are used as the blocking or diluting agents should be at least as rapidly absorbed and metabolized as their radioactive counterparts.

b. Mobilizing Agents

Mobilizing agents are compounds that enhance and increase the natural turnover processes of radioactive contaminants and thereby accelerate their release from tissues. They are most effective when given immediately following contamination, but they may retain some effectiveness for up to 2 weeks after contamination. Drugs that have been recommended for this purpose include antithyroid drugs, ammonium chloride, diuretics, expectorants and inhalants, parathyroid extract, and corticosteroids.[2,7,9] These agents require experienced consultation, treatment, and management and are not currently FDA approved as decorporation agents.

c. Chelating Agents

Chelators are substances that bind with certain metals to form a stable complex that can be more rapidly eliminated from the body via excretion by the kidneys. Diethylenetriaminepentacetate (DTPA), as the calcium or zinc salt, has been used as an investigational agent for many years in this capacity.[7,9,10,11,12,18] DTPA forms stable complexes with transuranium elements, and these complexes are renally excreted, thus decreasing body burden. The calcium and zinc salts of DTPA have both been used investigationally for the

[16] See the *Federal Register*, Vol. 66, p. 64066, (December 11, 2001.

[17] See FDA guidance *Potassium Iodide as a Thyroid Blocking Agent in Radiation Emergencies*, available at www.fda.gov/cder/guidance/4825fnl.htm.

[18] See Breitenstein BD, Fry SA, and Lushbaugh CC (1990), DTPA Therapy: The US Experience 1958-1987. In *The Medical Basis for Radiation Accident Preparedness*, edited by RC Ricks and SA Fry, Amsterdam, Elsevier Science Publishing Co

treatment of plutonium, americium or curium internal contamination under an IND (investigational new drug) application held by the Radiation Emergency Assistance Center/Training Site (REAC/TS). Ca-DTPA is administered as a single intravenous injection or inhaled dose as soon as possible after contamination and repeated doses of Zn-DTPA administered intravenously may be given daily as necessary as maintenance therapy. Based on a review of the data maintained by REAC/TS, in 2003 FDA determined that Ca-DTPA and Zn-DTPA, when produced under conditions specified in an approved NDA, can be safe and effective for the treatment of internal contamination with plutonium, americium, and curium.[19] At the same time, FDA announced the availability of a guidance document, *Calcium DTPA and Zinc DTPA Drug Products: Submitting a New Drug Application*, to assist manufacturers who plan to submit NDAs for Ca-DTPA and Zn-DTPA. Recently, FDA has approved NDAs submitted by Hameln Pharmaceuticals GmbH for Ca- and Zn-DTPA.

DTPAs bind uranium less well and are not expected to be effective for uranium contamination (see Ca-DTPA and Zn-DTPA product labeling at http://www.fda.gov/cder/drug/infopage/DTPA/default.htm). Uranium contamination has been treated with oral sodium bicarbonate, regulated to maintain an alkaline urine pH, and accompanied by diuretics.[2] Oral sodium bicarbonate has not been approved in the United States for this indication.

4. Potential Radioactive Contaminants and Possible Treatments

Radioactive contaminants of immediate medical significance and possible treatments are listed in the following table.

[19] See the *Federal Register*, Vol. 68, p. 53984, September15, 2003.

TABLE 1. RADIOACTIVE CONTAMINANTS WITH MEDICAL SIGNIFICANCE AND POSSIBLE TREATMENTS [20]

Radioactive Contaminant	Radiation Type[21]	Target Organ	Contamination Mode*	Treatment
Americium-241	α, γ	Bone	I/W	CaDTPA, ZnDTPA†
Californium-252	γ, α, η	Bone	I/W	CaDTPA, ZnDTPA†
Cerium-141, 144	β, γ	GI, lung	I/GI	CaDTPA, ZnDTPA†
Cesium-137	β, γ	Total body	I/S/GI	Prussian blue£
Curium-244	α, γ, η	Bone	I/GI	Ca-DTPA, Zn-DTPA†
Iodine-131, 132, 134, 135	β, γ	Thyroid	I/GI/S	KI ¥
Plutonium-239, 238	α, γ	Bone	I/W	CaDTPA, ZnDTPA†
Polonium-210	α	Lung	I	Dimercaprol‡
Strontium-89, 90	γ	Bone	I/GI	$AlPO_4$**
Tritium (^3H)	β	Total body	I/S/GI	Forced H_2O§
Uranium-238, 235, 239	α, β, γ	Bone	I/S/W	$NaHCO_3$***

* Contamination Mode: I by inhalation; GI by gastrointestinal absorption; S by skin absorption; W by wound absorption

** The antacid aluminum phosphate in gel form used as a gastrointestinal adsorbent for radiostrontium

*** Sodium bicarbonate to maintain alkalinity of urine used in conjunction with diuretics

† Calcium and Zinc DTPA, metal complexes of diethylenetriaminepentaacetate. Both are currently FDA approved. The calcium form is recommended for the first decontaminating dose, followed with the zinc form for subsequent doses.

‡ A mercury and arsenic poisoning chelation agent (very toxic)

¥ Agent blocking radioiodine absorption in tissues resulting in its dilution

§ Simple forced intake of water, resulting in tritium dilution

£ A dye used as an ion exchanger, currently FDA approved

E. Animal Efficacy Rule

In May 2002, FDA promulgated a rule allowing for approval of new drug and biological products based on animal data when adequate and well-controlled efficacy studies in humans cannot be ethically conducted because the studies would involve administering a potentially lethal or permanently disabling toxic substance or organism to healthy human volunteers, and

[20] Based on Cerveny, TJ (1989), Treatment of Internal Radionuclide Contamination. In *Textbook of Military Medicine, Part I, Medical Consequences of Nuclear Warfare; Warfare, Weaponry, and the Casualty*, Office of the Surgeon General, Department of the Army.

[21] The various types of radiation are described in the glossary.

field trials are not feasible prior to approval. The intent of the "Animal Efficacy Rule"[22] is to facilitate the development of medical countermeasures to treat or prevent injury from chemical, biological, nuclear, or radiological agents. The rule does not apply to products that can be approved based on other efficacy standards (e.g., accelerated approval based on surrogate markers or clinical endpoints other than survival or irreversible morbidity), nor does it address the safety evaluation of the products to which it does apply.

Emergencies may arise necessitating human use of a decorporation agent still under development and for which approval under the Animal Efficacy Rule is not immediately feasible. Should this situation arise, it is conceivable that the product could be used under FDA's investigational new drug regulations in 21 CFR Part 312 or under the emergency use authorization provision in § 564 of the Federal Food, Drug, and Cosmetic Act.

1. Applying the Animal Efficacy Rule to Decorporation Agents

For decorporation agents used to enhance elimination or excretion of absorbed radioactive contaminants, animal studies may be used to provide substantial evidence of effectiveness only when (1) there is a reasonably well-understood pathophysiological mechanism of the toxicity of the radioactive contaminant and its elimination or excretion by the decorporation agent, (2) the effect is demonstrated in more than one animal species expected to react with a response predictive for humans, unless the effect is demonstrated in a single animal species that represents a sufficiently well-characterized animal model for predicting the response in humans, (3) the animal study endpoint is clearly related to the desired benefit in humans, and (4) pharmacokinetic and pharmacodynamic data or information in animals and humans are sufficient to allow selection of an effective dose in humans. It should be noted that animal efficacy studies are subject to the same good laboratory practice (GLP) requirements as animal toxicology studies (see below).

In some situations, human efficacy studies using nontoxic levels of the radioactive contaminant or a stable, nonradioactive counterpart may be feasible and ethical. In such cases, approval could be based on efficacy standards described elsewhere in FDA's regulations, and evidence of effectiveness from animal studies alone would not be sufficient to support approval of a new product or a new indication for an already marketed product. Human efficacy studies would be needed to support marketing approval (*see* 21 CFR 314.600 and 601.90).

Even if a new decorporation agent is eligible for approval under the Animal Efficacy Rule, that agent must still be evaluated for safety in humans; animal data is not sufficient to demonstrate safety (21 CFR 314.600 and 601.90). Products evaluated for effectiveness under the Animal Efficacy Rule must be evaluated for safety under preexisting requirements for establishing the safety of new drug and biologic products (21 CFR 314.600 and 601.90). FDA believes that the safety of these products (unlike their effectiveness) can be studied in human volunteers.

[22] The Animal Efficacy Rule is codified in 21 CFR part 314, subpart I for human drug products and 21 CFR part 601, subpart H for human biological products.

2. Three Requirements for Approval under the Animal Efficacy Rule

Approval of a decorporation agent under 21 CFR part 314 subpart I and 21 CFR part 601 subpart H requires: (1) submission of a plan or approach to postmarketing studies that would be feasible should an accidental or intentional release of radiation occur, (2) postmarketing restrictions to ensure safe use, if deemed necessary, and (3) product labeling intended for the patient to be provided prior to product administration or dispensing, advising, among other things, that the product's approval was based on efficacy studies conducted in animals alone.

III. PRODUCT DEVELOPMENT PLAN FOR AN NDA, BLA, OR EFFICACY SUPPLEMENT

We recommend that a sponsor planning to develop a decorporation agent for submission as (1) a new drug application (NDA) or biologic license application (BLA), or (2) an efficacy supplement for a marketed product in support of a new use as a decorporation agent, meet with representatives of the Division of Medical Imaging and Radiopharmaceutical Drug Products and the Office of Counter-Terrorism and Pediatric Drug Development in CDER regarding the specifics of a product's development plans. This is particularly important if the sponsor intends to seek approval under the Animal Efficacy Rule.

A comprehensive search of the medical literature and available scientific databases may reveal important information regarding a product's chemistry, animal safety pharmacology, toxicology and efficacy, or human pharmacology and safety and inform the sponsor regarding additional studies that may be needed. Sponsors are encouraged to attempt to access primary data and perform an independent review of published findings to the extent possible. In most instances, literature references alone will not provide substantial evidence of effectiveness of a new product or new use, and additional well-controlled, animal efficacy and human pharmacology and safety studies will be needed.[23]

A. Study Sequence

A typical sequence for the requisite animal and human studies to support approval under the Animal Efficacy Rule is represented below. Additional detailed information is contained in the specified subsection.

- Search of the published literature and available scientific databases and review of source documents, if available

[23] See 21 CFR 314.54 and FDA's Citizen Petition Response (Dockets Nos. 2001P-0323/CPI & C5, 2002P-0447/CP1, and 2003P-0408/CP1), dated October 14, 2003, for a description of FDA's drug approval process under section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act. An applicant may rely on the literature and/or the Agency's previous finding of safety and effectiveness for a listed drug. Such reliance will be appropriate only to the extent that the proposed product in the 505(b)(2) application shares characteristics (active ingredient, dosage form, strength, route of administration, indications, and conditions of use) in common with the listed drug. The safety and effectiveness of any differences between the listed drug and the drug proposed in the 505(b)(2) application must be supported by additional data, including clinical or animal data as appropriate.

- Tests of effectiveness in vitro*;* assay development and validation (i.e, chemistry, manufacturing, and controls) (Subsection III.B)

- Preliminary or exploratory animal efficacy studies, typically in rodents or other suitable small animal model (Subsection III.C)

- Animal safety pharmacology and toxicology studies (Subsection III.D)

- Single-dose, dose escalation, safety, and tolerability studies in humans (initial first in human studies), using doses supported by animal data, as required (Subsection III.E)

- Selection of the most appropriate animal species for the definitive efficacy study, the one on which approval will be based; the animal species selected should be similar to humans with respect to the pharmacokinetic profile of the decorporation agent and the distribution of the radioactive contaminant.

- Efficacy study supporting approval, conducted in the most appropriate animal species (Subsection III.C)

- Safety studies in humans; FDA recommends that these studies be conducted at the highest dose anticipated to be marketed and be performed in parallel with the pivotal animal efficacy study, assuming the product is reasonably likely to produce clinical benefits in humans (Subsection III.F).

B. Chemistry, Manufacturing, and Controls

The same standards for chemistry, manufacturing, and controls (CMC) apply to decorporation agents as with other pharmaceuticals. We recommend sponsors consult the appropriate FDA guidances for drug substances, drug products, and biological products. We also recommend that sponsors consider developing pediatric-appropriate dosage forms (e.g., liquid preparations, powder formulations for suspension), as appropriate.

Specifications for new drug substances (also referred to as new chemical entities) and new indications for previously approved drug or biological products should be adequate for the intended dosage form and route of administration to ensure identity, strength, quality, purity and potency.[24]

FDA recommends that sponsors develop and validate in vitro tests intended to predict the effectiveness of isotope (radioactive or nonradioactive) uptake by a decorporation agent. FDA also urges sponsors to establish the time course of uptake, generally as part of the specification for product release and stability. For example, in the case of Prussian blue, FDA used the mass

[24] See International Conference on Harmonisation (ICH) guidance *Q6A Specifications: Test Procedures and Acceptance Criteria for New Drug Substances and New Drug Products: Chemical Substances*; and ICH *Q6B Specifications: Test Procedures and Acceptance Criteria for Biotechnological/ Biological Products.*

uptake of nonradioactive cesium per gram of Prussian blue as a function of time as a measure of its probable effectiveness. This in vitro test measures not only the total uptake of cesium, but also the kinetics of the solution to solid (heterogeneous) exchange reaction. The synthetic procedure for manufacturing Prussian blue can produce insoluble solids of highly variable particle size, porosity, hydration, and defect impurities. In FDA's experience, it was important to consider the effects of all of these factors on Prussian blue's cesium exchange properties.

C. Animal Efficacy Studies

Under the Animal Efficacy Rule, a sponsor can rely on animal studies to provide substantial evidence of effectiveness for certain new drug or biological products intended to reduce or prevent the toxicity of chemical, biological, radiological, or nuclear substances. Under 21 CFR 314.610(a)(2) and 601.91(a)(2), one of the requirements for approval based on effectiveness data from animals alone is that the effect is demonstrated in more than one animal species expected to react with a response predictive for humans, unless the effect is demonstrated in a single animal species that represents a sufficiently well-characterized animal model for predicting the response in humans. Determination of the number of animal studies needed to support approval of a particular NDA or BLA will be made on a case by case basis, as will the determination of what constitutes a sufficiently well-characterized animal model for a given product or indication. In FDA's experience, animal efficacy studies found in the published literature or conducted without the expressed purpose of supporting regulatory submissions have often lacked adequate scientific rigor. Furthermore, unless there are sufficient pharmacokinetic and/or pharmacodynamic data to conclude that a rodent species will adequately predict the human response, FDA believes that the effectiveness of a proposed decorporation agent will need to be demonstrated in a second, probably non-rodent, animal species.

1. Considerations Regarding the Efficacy Study Supporting Approval

We recommend that the following factors be considered in the design and interpretation of the animal efficacy study or studies that will support product approval (this list is not comprehensive):

1. Conducting the study in an appropriate animal species; the pharmacokinetic profile of the product and the distribution of the radioactive contaminant in the selected species should be similar to what is observed or expected in humans.

2. Inclusion of both male and female animals; the number of animals and the inclusion of appropriate controls should be adequate for proper statistical analysis.

3. Use of a test product that is pharmaceutically equivalent to that intended for humans.

4. Evaluation of a range of doses and calibration of a dose-response relationship.

5. Use of a dosing frequency and route of administration that are similar, if not identical, to that intended for humans; determination of the efficacy window (i.e., the timing of product administration relative to radioactive contamination and duration of treatment).

6. Efficacy can be based on direct measurement of the elimination of the radioactive contaminant through feces and/or urine (or exhalation, as appropriate) at various time points after administration of the decorporation agent; alternatively, measurement of the residual body burden may be evaluated. These measurements can then be used to calculate changes in *whole-body committed radiation dose* following product administration. It is generally acknowledged that the long-term risk of cancer is a function of the radiation dose received. Clinically meaningful reduction in *whole-body committed radiation dose* (see Glossary definition) following administration of a decorporation agent in the pivotal animal efficacy study or studies is "clearly related to the desired benefit in humans, generally the enhancement of survival or prevention of major morbidity" under 21 CFR 314.610(a)(3).[25]

7. Designing the study using the relevant characteristics of an adequate and well-controlled study as described in 21 CFR 314.126, including reduction of bias, a clear protocol, and a statistical plan. To support approval, the decorporation agent should demonstrate a statistically superior and clinically meaningful reduction in whole-body committed radiation dose compared to control.

2. Good Laboratory Practice (GLP) Compliance

Because efficacy studies will not be conducted in humans when a product is approved under the Animal Efficacy Rule, it is essential to ensure the quality and reliability of the animal efficacy data. Therefore pivotal efficacy studies supporting approval must be conducted in compliance with GLPs (see 21 CFR Part 58).

D. Animal Safety Pharmacology and Toxicology Studies

We urge sponsors to conduct animal safety studies to define pharmacological and toxicological effects prior to initiation of first-in-human clinical trials to establish a safe starting dose for decorporation agents that are new molecular entities (NMEs). FDA recommends that the product used for definitive animal safety pharmacology and toxicology studies be pharmaceutically equivalent to the product proposed for human studies. If the decorporation agent is a product that has already been approved for marketing, or if comprehensive animal or human data are available under another NDA or BLA that the sponsor either owns or has a right of reference to, additional safety pharmacology and toxicology studies may not be required, unless the route of administration, dosing regimen, and/or formulation is new.

1. Safety Pharmacology Studies

Safety pharmacology studies investigate potential undesirable pharmacodynamic effects on physiologic functions in relation to exposure in the therapeutic range and above. FDA

[25] Studies evaluating long-term cancer risk or survival following radioactive contamination may not be feasible or ethical and would generally not be required to support approval of a new decorporation agent or a new indication for a previously approved product.

recommends that sponsors perform safety pharmacology studies assessing effects on the cardiovascular, central nervous, pulmonary, and renal systems prior to first administration in humans.[26,27] Follow-up or supplemental studies may also be needed if there is cause for concern. Information from adequately designed and conducted toxicology studies that address safety pharmacology endpoints may result in reduction or elimination of some of the safety pharmacology studies.[26] For products that are not systemically absorbed, it may be necessary to conduct safety studies using intravenous administration to assess the potential risk that may arise in special populations (e.g., ulcerative colitis patients). FDA urges sponsors to thoroughly evaluate local gastrointestinal toxicity for such products.

2. Toxicokinetic and Pharmacokinetic Studies

FDA recommends that exposure in animals be evaluated prior to human safety studies.[28] FDA believes that absorption, distribution, metabolism, and excretion (ADME) data in animals should be available to compare human and animal pharmacokinetic profiles.

3. Toxicology Studies

FDA recommends that toxicology studies include the following:

- Expanded single- and repeat-dose toxicity studies in two mammalian species (one non-rodent). FDA recommends that the duration of the repeat-dose toxicity studies be equal to or exceed the duration of the intended treatment in humans.[29]

- Genotoxicity studies in vitro and in vivo[30,31]

- Reproductive toxicity studies (Segment I & II).[32,33] For oral decorporation agents that are not systemically absorbed, reproductive studies may not be needed.

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[26] See ICH guidance *S7A Safety Pharmacology Studies for Human Pharmaceuticals*, for further discussion of safety pharmacology study designs.

[27] See ICH guidance *S7B Safety Pharmacology Studies for Assessing the Potential for Delayed Ventricular Repolarization (QT Interval Prolongation) by Human Pharmaceuticals.*

[28] See ICH guidance *S3A Toxicokinetics: The Assessment of Systemic Exposure in Toxicity Studies.*

[29] See ICH guidance *S4A Duration of Chronic Toxicity Testing in Animals (Rodent and Nonrodent Toxicity Testing).*

[30] See ICH guidance *S2A Specific Aspects of Regulatory Genotoxicity Tests for Pharmaceuticals.*

[31] See ICH guidance *S2B Genotoxicity: A Standard Battery of Genotoxic Tests for Pharmaceuticals.*

[32] See ICH guidance *S5A Detection of Toxicity to Reproduction for Medicinal Products.*

[33] See ICH guidance *S5A Detection of Toxicity to Reproduction for Medicinal Products: Addendum on Toxicity to Male Fertility.*

- Local tolerance studies in animals using routes relevant to the proposed clinical route of administration. The assessment of local tolerance may be part of other toxicity studies.

- Safety studies in juvenile animals may be needed as decorporation agents are likely to be used in pediatric populations.[34]

- Carcinogenicity studies, typically needed only if there is cause for concern, such as evidence of preneoplastic lesions in repeat-dose toxicity studies

Any special toxicology study requirements will be determined on a case-by-case basis, depending on product characteristics. Animals used to determine efficacy may also be assessed for toxicity. For example, safety endpoints may include assessment of physiologic functions during the study, as well as determination of histology of tissues obtained at necropsy.

We recommend sponsors refer to the appropriate Agency guidances for information regarding (1) the conduct of safety pharmacology and toxicology studies, (2) the timing of these studies relative to the initiation of human studies, and (3) appropriate methods for dose extrapolation that may be used for estimating a safe starting dose in human clinical trials.[35]

E. Clinical Pharmacology and Biopharmaceutics Studies

Under 21 CFR 314.610(a)(4) and 601.91(a)(4)) of the Animal Efficacy Rule, the data or information on the kinetics and pharmacodynamics of a decorporation agent in humans, as well as in animals, must allow selection of an effective dose in humans. We recommend that sponsors attempt to evaluate as heterogeneous a human study population as possible, with a reasonable balance of males and females, young and elderly, and members of differing racial groups.

FDA believes that a complete clinical pharmacology and biopharmaceutics evaluation of a decorporation agent will provide detailed information on (1) general attributes, (2) general clinical pharmacology, (3) extrinsic and intrinsic factors, (4) general biopharmaceutics, and (5) bioanalytical methods. In particular, sponsors are urged to consider the following issues relating to these topics:

General attributes, including the physico-chemical properties of the drug substance and the formulation of the drug product.

General clinical pharmacology, including (1) the proposed mechanism or mode of action of the product and (2) the proposed human dosage regimen and its justification. FDA recommends that pharmacologic assessment address the following in detail:

[34] In 2003, the Agency issued the draft guidance for industry *Nonclinical Safety Evaluation of Pediatric Drug Products.*

[35] In 2002, FDA issued a draft guidance entitled *Estimating the Safe Starting Dose in Clinical Trials for Therapeutics in Adult Healthy Volunteers*. Once finalized, it will represent the Agency's thinking on this issue.

1. The basis for selecting the response endpoints in animal models and how they are extrapolated to humans; establishment of pharmacokinetic (PK)/ pharmacodynamic (PD) relationships in animals; time to the onset and offset of the pharmacological response
2. Product absorption, distribution, metabolism, and excretion in humans (a mass balance study using radiolabeled product would be useful in this regard). FDA believes that the route of administration should be designated and be the same in both animal and human studies.
3. Identification and quantification of the active moieties in plasma (or other appropriate biological fluid) and characterization of pharmacokinetic parameters in humans, including the following:
    - The degree of linearity or nonlinearity in the dose-concentration relationship evaluated in a dose escalation study
    - The change in pharmacokinetic parameters with time following multiple dosing, if multiple dosing is indicated
    - The metabolic profile, pharmacokinetic parameters, and plasma protein binding in humans as compared to animals
    - Characteristics of the exposure-response relationships (i.e., dose-response or concentration-response) for safety parameters

Extrinsic and intrinsic factors, including the effect of age, gender, race, and organ dysfunction (e.g., renal impairment and hepatic impairment) on exposure-response relationships, as necessary; evaluation of drug-drug interactions, as appropriate

General biopharmaceutics, including the solubility, permeability, and dissolution of the drug product, if applicable; the effect of food on bioavailability of the drug product, if applicable

Bioanalytical methods for determination of active moiety and metabolite(s), including methods to assess metabolite concentrations. FDA recommends that sponsors provide the rationale for selecting metabolites for analysis and describe the range of the standard curve and curve fitting techniques. FDA also recommends that sponsors identify the upper and lower limits of quantification (ULOQ/LLOQ) and describe the accuracy, precision, and selectivity of analytical methods at these limits. Sponsors are also urged to address sample stability during freeze-thaw cycles, sample transport, and long-term storage.

F. Safety Assessment in Humans

The goal of human safety studies is to characterize the adverse effects of the product in humans, so that this toxicity can be weighed to the extent possible against the benefits of use, both generally and for particular patients. When designing safety studies for decorporation agents that may be approved under the Animal Efficacy Rule, the sponsors are urged to consider the following:

1. What safety information should be generated preapproval, and in particular, what specific safety risks or animal findings should be explored preapproval?

2. What safety information reasonably may be delayed to postmarketing studies?

Considerations for Safety Studies Supporting Approval. At a minimum, FDA urges sponsors to conduct a randomized, placebo-controlled safety study in humans to support approval of a product under the Animal Efficacy Rule. Additional safety studies may be needed to address specific concerns not addressed by, or raised by, the results of the placebo-controlled trial. Sponsors are encouraged to consider the following factors in the design and interpretation of human safety studies that will support product approval (this list is not comprehensive):

1. Enrollment and assessment of a sufficient number of adult male and female subjects to allow for proper statistical analysis

2. Use of a test product that is bioequivalent to, and delivered by the same route of administration and dosing regimen as, that intended for marketing

3. Evaluation of a range of doses and establishment of a dose-response relationship

4. Inclusion of complete physical examinations with vital signs and laboratory parameters (e.g., electrolytes, chemistry and hematology profiles, tests of renal and liver function) as part of the clinical evaluation. Additional evaluations may be needed, as appropriate. FDA recommends that evaluations be performed at baseline and at specified follow-up time points, as dictated by the dosing regimen and preclinical or other available human safety findings.

5. Incorporation of population PK/PD studies using sparse sampling techniques (i.e., three to four data points per subject). Such studies may be useful in identifying factors causing intersubject variability and in relating individual drug exposure to safety outcomes.

6. Monitoring for adverse events that includes collection of the following: the timing of the event relative to product administration, the duration and severity of the event, clinical management of the event, outcomes (e.g., need for hospitalization, event resolved spontaneously)

In 2004, the Agency published a draft guidance, *Premarketing Risk Assessment,* which addresses preapproval risk assessment in more detail, including generation, analysis, and presentation of human safety data in an application for approval.

Size of the NDA or BLA Safety Database. We recommend that a sponsor planning to submit an NDA or BLA for a new decorporation agent, or an efficacy supplement for a previously marketed product in support of a new use as a decorporation agent, under the Animal Efficacy Rule or other regulatory mechanism, meet with the appropriate representatives in CDER to discuss the size of the human safety database. The following factors may increase or decrease the size of the requisite NDA or BLA safety database (this list is not comprehensive):

1. Whether additional studies focused on risks to a specific target organ or addressing specific animal or clinical safety concerns are needed preapproval

2. Whether the product is intended to treat otherwise healthy individuals on a large scale or a defined, seriously ill subpopulation for whom some risk would be acceptable

3. Whether the product will be used chronically or for acute, one time only use

4. Whether the product treats a condition for which there are no available therapies

5. Whether the product meets an unmet medical need (e.g., is superior in efficacy to or avoids serious toxicities associated with available therapies, or provides benefits to patients who are unresponsive to or intolerant of available therapies)[36]

6. Whether the product is already marketed and known to have an acceptable safety profile for the populations that would receive a decorporation agent

7. Whether the product is first in its class or relatively similar to other products on the market

An NDA or BLA safety database generally will include human subjects exposed to a variety of product doses as well as placebo-treated subjects. Although the requisite number of subjects may vary across applications for reasons cited above, FDA believes that in many cases 200 to 300 subjects who (1) have been exposed to the decorporation agent at doses and durations comparable to those anticipated in marketed use and (2) have had a minimum battery of safety testing, will be sufficient to support approval.

G. Benefit-Risk Assessment

Benefit-risk assessment relates the potential or actual benefit that a particular patient or population derives from using a product to the risks incurred through its use. If a decorporation agent is highly effective in eliminating absorbed radiocontaminants from the body and is relatively free of risk, its benefit-risk assessment would be highly favorable. Such a product would provide enormous benefit, especially to those most heavily exposed to radioactive contamination, or to those who might suffer greater consequences as a result of even lesser amounts of exposure (e.g., pediatric populations). Situations may arise, however, in which there is a question of whether or not to administer such a product to a less heavily exposed population. Therefore, there is a great need for a careful assessment of benefit-risk in populations with varied levels of radioactive contamination. If a product's approval is subject to the Animal Efficacy Rule, prior to its approval such assessments will generally be based primarily on experience with animal models. In the event of accidental or nonaccidental radioactive contamination, serious efforts to evaluate the benefit-risk of a decorporation agent in humans should be made, to the extent possible.

[36] See FDA guidance for industry *Available Therapy.*

IV. POSTAPPROVAL COMMITMENTS FOR PRODUCTS APPROVED UNDER THE ANIMAL EFFICACY RULE

Sponsors planning to submit an NDA or BLA for a new decorporation agent, or an efficacy supplement for a marketed product in support of a new use as a decorporation agent, for approval under the Animal Efficacy Rule[22] are encouraged to meet with the appropriate representatives in CDER regarding the specifics of postapproval commitments. Postapproval issues for products approved under the Animal Efficacy Rule are discussed at 21 CFR 314.610(b) (for drugs)and 21 CFR 601.91(b) (for biological products).

One of the requirements for approval under the Animal Efficacy Rule is that sponsors must conduct postmarketing studies to verify and describe a decorporation agent's clinical benefit and to assess its safety when used as indicated when such studies are feasible and ethical (see 21 CFR 314.610(b)(1) for drug products and 21 CFR 601.91(b)(1) for biological drug products). Except in the case of accidental or nonaccidental radioactive contamination, such studies would be infeasible. Under the rule, sponsors must, therefore, include as part of their NDA, BLA or efficacy supplement a plan for conducting postmarketing studies. Such studies could include field studies of subjects with radioactive contamination.

To the extent possible, postmarketing studies conducted after accidental or nonaccidental radioactive contamination may be useful for addressing safety and efficacy concerns for populations that were not studied or were only studied to a limited degree preapproval, including (1) pediatric populations, (2) the elderly, (3) pregnant or lactating women, (4) subjects with hepatic or renal impairment, (5) subjects of different ethnic or racial backgrounds, or (6) subpopulations with genetic polymorphisms.

At a minimum, FDA recommends that sponsors design postmarketing studies to collect the following information on subjects with radioactive internal contamination[37]:

- The date of the occurrence, and the cause for and extent of the initial contamination
- The radiocontaminant(s) involved
- Demographic information on the subject(s), including age, gender, and race/ethnicity
- The initial clinical status of the subject(s) immediately after contamination
- Pertinent medical history of the subject(s)
- The estimated total body radiation in cGy
- Ancillary methods used in decontamination, if any

[37] See e.g., the "Prussian Blue Patient Treatment Data Form" included in the professional labeling for Radiogardase (Insoluble Prussian Blue capsules) for the kinds of information that may be collected in the event of a radiation accident or terrorist attack. The professional labeling for Radiogardase is available at http://www.fda.gov/cder/foi/label/2003/021626lbl.pdf

- Details on the decorporation agent(s) used, including the dose, frequency, timing of administration relative to the initial contamination, duration of therapy, and reasons for premature discontinuation if this occurs
- Other pharmaceutical or detoxifying agents used, if any
- Any beneficial outcomes observed, including evidence for reduction in internally absorbed radiocontaminant(s)
- Any adverse events, not just those deemed product-related
- Any short- and long-term serious outcomes observed (e.g., death, hospitalization, cancer diagnosis)

GLOSSARY

Alpha Particles. Alpha particles are helium nuclei, charged particles with a mass four times that of a neutron. Because of their mass and charge, alpha particles penetrate short distances and are fully stopped by the dead layers of the skin or by clothing. Alpha particles are a negligible external hazard, but become hazardous when internalized through inhalation, ingestion, or wounds. Alpha particles can cause as much as 10 times more damage to tissue per unit dose than gamma rays.

Beta Particles. Beta particles are electrons, charged particles that are emitted by several radiocontaminants present in fallout. These particles can travel a short distance in tissue; if large quantities are involved, they can produce damage to the basal stratum of the skin. The lesion produced, a "beta burn," can appear similar to a thermal burn.

Blocking and Diluting Agents. Medical products that decrease the likelihood of radiocontaminant absorption by decreasing its availability.

Chelating Agents. Medical products that bind with certain metals more strongly than others to form a stable complex that, when soluble, can be more readily excreted by the kidneys.

Committed Radiation Dose. The total radiation dose accumulated in an organ or tissue over time, usually 50 years for adults and 70 years for children. The magnitude of the dose depends on the amount of ingested radioactive material and the time it stays in the body. Whole-body committed dose is the sum of weighted radiation doses in all the organs and tissues of the body.

Decorporation Agents. Medical products that increase the rate of elimination or excretion of absorbed, inhaled, or ingested radiocontaminants.

Gamma Rays. Ionizing radiation emitted from many radiocontaminants. Gamma rays are a form of uncharged radiation similar to x-rays. X-rays cannot be distinguished from gamma rays when they are the same energy. Their differences are due to their origin. Gamma rays are intranuclear in origin, while x-rays are extranuclear. Both are highly energetic and pass through matter easily. Because of their high penetrability, gamma radiation can result in whole-body exposure from external sources.

Gray (Gy). The Standard International (SI) unit of absorbed radiation dose equal to 1 joule of energy absorbed per kg of mass. 1 Gy is equal to 100 rads. The rad was replaced by the Gy.

Mobilizing Agents. Medical products that enhance and increase the natural turnover processes and thereby induce the release of radiocontaminants from tissues.

Neutrons. Neutrons are uncharged particulate radiation. Compared to gamma rays, neutrons can cause twenty times as much damage to tissue per unit dose.

Rad. Acronym for ***r***adiation ***a***bsorbed ***d***ose. The old unit of measurement of the radiation absorbed dose corresponding to an energy transfer of 100 ergs per gram of any absorbing

material including tissues. The rad has been replaced by the Standard International SI unit of Gray, 1 joule/kilogram, and 1 Gy is equal to 100 rads.

Radiological Dispersal Device or RDD. Sometimes referred to as a "dirty bomb," a radiological dispersal device is any device that causes the purposeful dissemination of radioactive material across an area using conventional (non-nuclear) explosives. The radioactive composition of the dispersed radioactive material usually will be unknown until an assessment is made by qualified personnel.

Radiation. Ionizing radiation may consist of alpha particles, beta particles, or neutrons, which are particulate; x-rays, gamma rays, or photons which are electromagnetic in nature.

X-rays. Electromagnetic radiation, photons, similar to gamma rays. X-rays and gamma rays do not differ from one another when they are the same energy. X-rays are produced extranuclearly, either from the deceleration of a high-energy electron usually associated with a machine, or from an internal energy transition from a higher to a lower state within an atom, referred to as characteristic x-rays. X-rays from such internal transitions are not considered hazardous relative to other emissions.

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